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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,729	07/13/2006	Neil Cashman	15289-8	7149

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
06/22/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,729	CASHMAN ET AL.	
	Examiner	Art Unit	
	CHANG-YU WANG	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,11-14,17,20-22,30,39,41,47-49,51,52 and 54-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52, and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/29/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 3/29/10 is acknowledged. Claims 3-10, 15-16, 18-19, 23-29, 31-38, 40, 42-46, 50, and 53 are cancelled. Claims 1, 2, 20-22, 39, 41, 47-49, 51-52 and 56 are amended. Claims 1, 2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52, and 54-56 are pending and under examination with respect to prion, BSE, peroxynitrite and antibody in this office action.

2. Applicant's arguments filed on 3/29/10 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

3. The objection to claims 1, 39, 49 and 56 is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1-2, 9, 11-14, 16-17, 20-22, 29-30, 39, 41, 47-49 and 51-56 under 35 U.S.C. 112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1-2, 9, 11-14, 16-17, 20-22, 29-30, 39, 41, 47-49 and 51-56 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1-2, 9, 11-14, 16-17, 20-22, 29-30, 39, 41, 47-49 and 51-56 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-22 of U.S. Patent No. 7041807 is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1-2, 9, 11-14, 16-17, 20-22, 29-30, 39, 41, 47-49 and 51-55 under 35 U.S.C. 102 (b) as being anticipated by US2002/0123072 (Prusiner et al. published Sep 5, 2002) is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 under 35 U.S.C. 102 (e) as being anticipated by US6677125 (Prusiner et al. issued Jan 13, 2004, priority Oct 9, 1998) is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1-2, 9, 11-14, 16-17, 20-22, 29-30, 39, 41, 47-49 and 51-55 under 35 U.S.C. 102(e) as being anticipated by US7041807 (Cashman et al., issued May 9, 2006, priority Jun 23, 1999) is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1, 2, 9, 11-14, 16, 17, 20-22, 29-30, 41, 47-48, 51-55 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's amendment to the claims.

Claim Rejections

4. Claim 22 is objected to because of the following informalities: BSE and CJD are not common abbreviations in the art. Applicants are required to spell out BSE and CJD at the first usage. Appropriate correction is required.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 3/29/10.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52, and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over either US2002/0123072 (Prusiner et al. published Sep 5, 2002, cited previously) or US6677125 (US6677125 is an issued patent of US2002/0123072, issued on Jan 13, 2004, priority Oct 9, 1998, cited previously) in view of US Patent No. 6765088 (Korthe et al, issued on Jul 20, 2004, as in IDS), Otvos et al. (Curr. Protein Pept. Sci. 2002 Dec; 3: 643-52) and Lehto et al. (Society for Neuroscience Annual Meeting; Aug 21, 2002, Program No. 692.9, Abstract, as in IDS). The citation from the primary reference in the rejection is based on US2002/0123072.

Claims 1, 2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52, and 54-56 as amended are drawn to a method of detecting whether a prion polypeptide including a target epitope recognized by an antibody designated as 3F4 and/or an antibody desginated as

6H4 is in i) a wild-type or ii) aggregated or misfolded conformation in a sample, comprising contacting the Prion polypeptide with peroxynitrite to block an accessible epitope wherein in the wild type conformation, the target epitope is accessible and reacts with peroxynitrite; and wherein in the aggregated or misfolded conformation, the target epitope is inaccesible and the target epitope cannot react with peroxynitrite, removing the unreacted peroxynitrite, disaggregating or denaturing the candidate to convert any inaccessible target epitope to accessible target epitope and contacting the prion polypeptide with an aptamer or antibody to determine whether the prion polypeptide is in a wild type or in an aggregated or misfolded conformation. Claim 49 as amended is drawn to a similar method as set forth above except that wherein in the wild type conformation, the target epitope is inaccessible and cannot react with the peroxynitrite; and wherein in the aggregated or misfolded conformation, the target epitope is accessible and reacts with peroxynitrite.

US2002/0123072 or US6677125 (Prusiner) teaches a method of detecting the presence of a disease related to confirmation of a protein PrP^{Sc} in a sample using an antibody specific for PrP^{Sc} such as 3F4 or antibodies in WO97/10505 as in instant claims 1, 2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52, and 54-56 (see p. 4, [0042]-p. 5, [0049]; p.6, [0089]-p.7, [0097] ; p. 11-14, examples 1-4; p.15, claims 1-27, in particular). Prusiner teaches that samples including biopsy or autopsy tissue, brain, spinal cord, peripheral nerves, muscle, cerebrospinal fluid, blood and blood components, lymph nodes, and in animal- or human-derived cultures (claim 30) are pre-treated and treated

with acid, chemical or chaotropic salts, denaturing detergents, guanidine hydrochloride or proteinase (claims 11, 13, 14, 54, 55) to denature or unfold proteins, which meets the limitation of contacting an agent to block or to convert an accessible target epitope into accessible target epitope as recited in instant claims 1-2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52 and 54-56 (see p. 7, [0098]-p.8, [0103], in particular). Prusiner teaches detection of native PrP^{c} (non-disease related conformation) or denatured form of PrP^{Sc} (disease-related conformation) with an antibody against PrP using immunoprecipitation or ELISA or time-resolved dissociation-enhanced fluorescence as recited in instant claim 41 (see p. 3, [0022]; p. 8, [0106]-p.9,[0116], in particular). Prusiner teaches pretreatment of samples with antibodies binding to the non-disease conformation of the protein and remove the non-disease protein or pretreatment of samples with acids or alkaline or temperature or chemicals to destroy proteins that are not related to the assayed proteins as in claims 1, 11-14, 30,39, 49 and 51 (see p. 7, [0099], in particular). Prusiner teaches antibodies binding to PrP^{Sc} including antibody 3F4 as recited in instant claims 1, 17, 39, 49 and 56(see p.9, [0110]-[[0116], in particular). Prusiner teaches detection of more PrP^{sc} in denature form of PrP (i.e. aggregated or misfolded conformation and then disaggregating or denaturing) than in native form with selected antibodies such as 3F4 as in claims 1, 2, 12, 17, 39, 47-49, (see p.9, [0110]-[[0116], in particular) and also teaches detection of aggregated or misfolded conformation of PrP as an indicator of prion disease comprising BSE or CJD as recited in instant claims 2 and 20-22 (see p. 8, [0107]-p.9, [0109], in particular).

Taken together, Prusiner teaches a method of detecting the presence of a non-disease related conformation of the protein PrP^{C} (wildtype conformation) and a disease related to conformation of a protein PrP^{Sc} (aggregated or misfolded conformation) in a sample using an antibody specific for PrP^{Sc} such as 3F4 or antibodies in WO97/10505 as in instant claims 1, 2, 11-14, 17, 20-22, 30, 39, 41, 47-49, 51, 52, and 54-56 (see p. 4, [0042]-p. 5, [0049]; p.6, [0089]-p.7, [0097] ; p. 7, [0098]-p.8, [0103]; p. 11-14, examples 1-4; p.15, claims 1-27, in particular). Prusiner's assay teaches the step of contacting the Prion polypeptide with an agent that reacts with and blocks an accessible target epitope or convert an inaccessible target to an accessible target as recited in independent claims 1, 39, 49 and 56 (accessible to in accessible) because Prusiner teaches pretreatment of samples with antibodies binding to the non-disease conformation of the protein and remove the non-disease protein or pretreatment of samples with acids or alkaline or temperature or chemicals (i.e. chemical modifying agent that chemically reacts with or converts the target epitope) to destroy proteins that are not related to the assayed proteins as in independent claims 1, 39, 49 and 56 and dependent claims 11-14, 47-48, 51, 54 and 55 (including non-elected species in claim 9) (see p. 7, [0099], in particular).

Prusiner does not teach the use of peroxynitrite to block an accessible target epitope or to convert inaccessible to accessible (or accessible to inaccessible) and does not teach 6H4 antibody to recognize PrP as recited in claims 1, 17, 39, 49 and 56.

US Patent No. 6765088 teaches different antibodies that recognize PrP^{Sc} including 6H4 and the method of using 6H4 to detect PrPSc and diagnosis of a prion

disease comprising CJD (see col. 9, lines 17-30; col. 12-col.13,line 48, col. 16-17, examples 13-15, in particular)

Otvos et al. teach that post-translational modifications play roles in the transformation of PrP^{c} (non-disease-related conformation to PrP^{SC} (disease-related conformation Human PrP contains two consensus sites for N-linked glycosylation, at Asn181 and Asn197 (see abstract, in particular). Otvos et al. teach that glycosylation can modify either the conformation of PrP^{c} or the stability of PrP^{SC} and, hence, the rate of PrP^{SC} clearance (see abstract, in particular). Otvos et al. teach that histochemistry for nitrotyrosine is used for detection of neuronal labeling, a sign of a peroxynitrite-mediated neuronal degradation and a marker for nitrative stress in scrapie-infected mouse brains. Otvos et al. teach that the post-translational modifications alone, or in combination with amino acid changes, play dominant roles in the pathogenic transformation of PrP^{c} to PrP^{sc}(see abstract, in particular).

Lehto et al. teach that recombinant mouse prion protein (rmPrP) treated with low concentrations of denaturants at low pH is reminiscent of the misfolded disease-associated prion protein isoform, PrP^{Sc}, and the conversion of rmPrP is associated with increased solvent accessibility of tyrosyl side chains. Lehto et al. also teach that treatment of normal brain homogenate with acid and denaturants causes PrP to become detergent insoluble. Lehto et al. teach that in order to probe the surface accessibility of tyrosine and other residues in normal and misfolded PrPC, normal and acid-misfolded human brain tissue was treated with the nitrating compound peroxynitrite. Lehto et al. further teach that peroxynitrite treatment of brain tissue

caused a reduction in the binding of the anti-PrP antibodies 3F4 and 6H4 in both immunoblotting and immunoprecipitation. Lehto et al. teach that peroxynitrite-induced epitope obscuration was more pronounced on normal brain PrP than on misfolded PrP, and the similar findings were observed in normal and scrapie-infected hamster brain, in which 3F4 and 6H4 epitopes of scrapie brain PrP were partially protected from peroxynitrite-induced nitration. Lehto et al. teach that immunoprecipitation of peroxynitrite-treated brain with anti-nitrotyrosine antibodies confirmed that PrP is nitrated on tyrosine residues in both normal and acid-misfolded, and scrapie brain PrP.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of US2002/0123072 or US6677125 (Prusiner), US6765088, Otvos et al. and Lehto et al. to use 6H4 anti-PrP^{Sc} antibody to detect epitopes on PrP^{Sc} and to use peroxynitrite to replace the agent that converts the accessible (or inaccessible) to inaccessible (or accessible) epitopes on PrP^{c} or PrP^{Sc} in the method of Prusiner. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because 6H4 anti-PrP^{Sc} antibody has been used to detect PrP^{Sc} and diagnose Prion disease as taught by US6765088, nitrotyrosine has been shown to detect scrapie-infected mouse brains (a sign of peroxynitrite-mediated neuronal degradation and a marker for nitrative stress in scrapie-infected mouse brains) as taught by Otvos et al. and peroxynitrite has been shown to block the interaction between the anti-PrPSc antibody and PrPSc and to convert the accessible (or inaccessible) to inaccessible (or accessible) epitopes on PrP^{c} or PrP^{Sc} as taught by Lehto et al.

Conclusion

6. NO CLAIM IS ALLOWED.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
June 7, 2010

/Christine J Saoud/
Primary Examiner, Art Unit 1647